Alzheimer’s Disease: Past, Present and Future

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Disclosures

• Consultant/Advisory Boards:
  – Elan/Wyeth, Genzyme, Helicon Therapeutics, Lilly, Janssen, Merck, Novartis, Pfizer

• Clinical Trials:
  – Baxter, Elan, Janssen, Novartis, Pfizer
Objectives

- Identify two therapeutic or preventative treatments currently in clinical trials.
- State biomarkers that influence screening and pharmacotherapy of Alzheimer’s Disease.

Overview

- A behavioral case study
- From rare disease to population crisis
- Risk factors: genes, lifestyle, the overlap with vascular risks, and the concept of “cognitive reserve”
- The continuum of pathological changes
- Imaging and biomarkers of the continuum of change: leveraging biomarkers against the limits of clinical detection
- Amyloid imaging: in vivo detection and its role in the continuum
- Therapies for amyloid, tau/neurofibrillary tangles and beyond...
- In the 25th anniversary year of the McKhann Criteria for AD, new criteria emerge--for AD, MCI, and preclinical detection
- With apologies to the Rolling Stones...Time is (not) on our side...
Case Study

46 year old married female
- General good health; on no medications
- No major medical problems
- Sub-acute onset of pathological jealousy
- Onset of naming problems (calls a pitcher a ‘milk pourer’)
- Difficulties with short term memory
- General medical examination normal
- Neurological examination normal except for mental status
- Progressive cognitive decline, death 4 years later

“Alzheimer’s original patient: Auguste D.

“I have lost myself.”
Alzheimer’s Disease

Memory loss
Language disturbances
Visuospatial deficits
“Frontal-Dysexecutive”:
  Impaired judgment, motivation, insight, decreased social cognition
Neuropsychiatric symptoms:
  depression, anxiety, sleep disturbance, psychosis

The anatomical/circuitry correlates of these behaviors are now largely identified

From Clinic to Community: characterizing the clinical picture of AD

Alois Alzheimer
Germany, 1907:
• single case report
• rare, unusual disease of middle-aged
• “pre-senile dementia”

Martin Roth and colleagues
Newcastle, 1964-70:
• community survey
• fairly common disease of elderly
• “senile dementia”

*Majority of cases of dementia in late life are AD, with many cases showing additional diseases, especially vascular disease*
1976 Katzman editorial: an alarm is sounded


- Predicted a massive increase in the number of cases of Alzheimer’s Disease in the 21st century

- No clear difference between presenile and senile onset with respect to symptoms or pathology

- Stimulated research in aging and AD brain

Change in Number of Deaths

Source: Alzheimer’s Association 2011 Alzheimer's Disease Facts and Figures
National Institutes of Health Research Funding

- Cancer: $5.8 Billion
- Heart Disease: $4.3 Billion
- HIV: $3.1 Billion
- Alzheimer's: $0.45 Billion

Source: Alzheimer's Association calculations based on NIH data

Alzheimer’s Prevalence, Its Projected Cost to Medicare and Medicaid, and Alzheimer’s Federal Research Funding

Source: Alzheimer’s Study Group, A National Alzheimer’s Strategic Plan, 2009.
Why Prevention is important:
5 years of delay of onset equals a 50% decrease in prevalence

Delay (years)
- 0
- 0.5
- 1
- 2
- 5

U.S. Prevalence of AD (millions)


Number of Alzheimer’s Cases 1950

Note: Each dot represents 100,000 cases of Alzheimer’s

Source: United National Population Database and Age Wave calculation
Vascular factors that increase AD risk

- Hypertension
- Hypercholesterolemia
- Diabetes mellitus
- Obesity
- Lack of exercise
- Inflammatory states, increased CRP
- Homocysteine elevation
- Carotid & Circle of Willis stenosis
### Genetics: 3 Mutations CAUSE AD;
*all 3 disrupt amyloid metabolism*

<table>
<thead>
<tr>
<th>Location</th>
<th>Gene Product</th>
<th>Effect on Amyloid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome 21</td>
<td>amyloid precursor protein (APP)</td>
<td></td>
</tr>
<tr>
<td>Chromosome 14</td>
<td>Presenilin 1 (PS1)</td>
<td><em>All 3 mutations raise serum levels of APP and Aβ</em></td>
</tr>
<tr>
<td>(transmembrane protein; part of γ-secretase complex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosome 1</td>
<td>Presenilin 2 (PS2)</td>
<td></td>
</tr>
<tr>
<td>(Volga German Kindreds)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Dose</td>
<td></td>
<td>Serum levels of APP &amp; Aβ are increased 1.5x</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>1.5x normal gene dose</td>
<td></td>
</tr>
<tr>
<td>(Down Syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Alleles</td>
<td></td>
<td><em>Diminished Aβ Clearance. Gene dose effect: 3 &amp; 8-12x risk for het &amp; homozygotes</em></td>
</tr>
<tr>
<td>Chromosome 19</td>
<td>apolipoprotein E (ApoE)</td>
<td></td>
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</tbody>
</table>

### APOE and Alzheimer’s Disease

#### ALLELE FREQUENCY:

<table>
<thead>
<tr>
<th>Allele</th>
<th>normal population</th>
<th>in AD</th>
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</thead>
<tbody>
<tr>
<td>E2</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>E3</td>
<td>79%</td>
<td>40-50%</td>
</tr>
<tr>
<td>E4</td>
<td>14%</td>
<td>40-50%</td>
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*Potential mechanisms:*
- Impaired removal of beta amyloid
- Diminished neural regeneration
- Allele frequency twice as high in Africans & African Americans as in Caucasians
The “Continuum” of AD

Clinical State

Normal  Pre-symptomatic AD  Mild Cognitive Impairment  AD

Disease Progression

Intervention

Primary Prevention  Secondary Prevention/Early Tx  Treatment

Normal  Pre-symptomatic AD  Mild Cognitive Impairment  AD

Brain Pathologic State

No Disease  No Symptoms  Early Brain Changes  No Symptoms  AD Brain Changes  Mild Symptoms  Mild, Moderate, or Severe Impairment

Disease Progression
Major Pathological Changes in AD

- **Brain shrinkage** (atrophy)
- **Neuritic (amyloid) Plaques**
  - altered metabolism of APP
  - Deposition of beta amyloid
- **Neurofibrillary Tangles**
  - Cytoskeletal pathology [girders and trusses]
  - Altered metabolism of tau protein
- **Neuronal death** in specific brain regions (why some regions and not others?)
- **Brain inflammation**
- **Region-specific neurotransmitter deficits** (especially ACh, 5HT, NE, glutamate)

NeuroFibrillary Tangles & Neuritic Plaques: Modern Techniques

The ‘inflammatory surround’ consists of distorted and degenerating synaptic processes, activated microglia, and astrocytic processes.
Amyloid Metabolism: “cut the grass”

- Amyloid Precursor Protein (APP)
- Presenilin 1/2
- APH-1
- PEN-2
- Nicastrin

Monomers $\rightarrow$ Dimers $\rightarrow$ Oligomers

Soluble Ab (1-40, 1-42)

Aggregation

Amyloid plaques, Inflammation, Neuron loss

Amyloid Metabolism:

- $\alpha$ site
- $\beta$ & $\gamma$ cleavage
- $\gamma$-cleavage site
- Presenilin 1/2
- APH-1
- PEN-2
- Nicastrin

Monomers $\rightarrow$ Dimers $\rightarrow$ Oligomers

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$\alpha$ site

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Monomers $\rightarrow$ Dimers $\rightarrow$ Oligomers

Soluble Ab (1-40, 1-42)

Aggregation

Amyloid plaques, Inflammation, Neuron loss

Amyloid Precursor Protein (APP)
Amyloid Metabolism: “cut the grass”

- Major lesion of Alzheimer’s disease and other neurodegenerative diseases
- Found inside neurons
- The paired helical filaments are the microtubule associated protein tau in an abnormally phosphorylated state
- Highly insoluble
- Associated with neuronal death
- Good correlation with cognitive impairment
Tau (Microtubule Associated Protein MAP2): Axonal Dissolution and Dysfunction in AD

Evolution of Neuroimaging in AD

• Computed Tomography
• MRI
• Volumetric MRI
• Co-registration of MRI
• Functional MRI
• FDG Glucose PET
• Amyloid Imaging


Brain Maps: Alzheimer’s Disease Spreading

Initially 6 months later 12 months later 18 months later

www.loni.ucla.edu/~thompson/AD_4D/dynamic.html.

Role of Biomarkers

• Diagnosis:
  – Evidence of amyloid says AD is present
• Prediction of progression from MCI to Alzheimer’s dementia:
  – If the amyloid is there in a person with memory loss who does not meet criteria for dementia, they have the Alzheimer process in their brain
  – Very likely the cause of symptoms is AD
  – Useful in prediction of progression
Biomarkers: Good Enough to Help Earlier Diagnosis in Research

Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria


The NINCDS-ADRDA and the DSM-IV-TR criteria for Alzheimer’s disease (AD) are the prevailing diagnostic standards in research; however, they have now fallen behind the unprecedented growth of scientific knowledge. Distinctive and reliable biomarkers of AD are now available through structural MRI, molecular neuroimaging with PET, and cerebrospinal fluid analyses. This manuscript provides the impetus for our proposal of revised diagnostic criteria: they stipulate that there must also be at least one or more abnormal biomarkers among structural neuroimaging with MRI, molecular neuroimaging with PET, and cerebrospinal fluid analysis of amyloid β or tau proteins.

Lancet Neurol 2007; 6: 734–46

Cerebrospinal Fluid (CSF) in Alzheimer’s Disease: Low Aβ and High Tau

<table>
<thead>
<tr>
<th>Concentration (pg/mL)</th>
<th>AD Patients</th>
<th>Control Patients</th>
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<tbody>
<tr>
<td>Aβ</td>
<td>500</td>
<td>100</td>
</tr>
<tr>
<td>Tau</td>
<td>700</td>
<td>200</td>
</tr>
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</table>

CSF in MCI has elevated tau, decreased β-amyloid

Hansson et al., 2006

The best markers across a broad range are MRI and FDG-PET. Amyloid imaging is the diagnostic marker.
Imaging Amyloid *in vivo* in Humans

- Amyloid Cascade **Hypothesis:**
  - Amyloid deposition begins years before clinical sx

- Ability to image brain amyloid will impact:
  - Diagnosis, Prognosis, Efficiency of drug development
  - 

- Current ligands; more are in development:
  - Flutametamol (PiB; GE), Florbetapir (*Amyvid*; Lilly), Florbetaben (Piramal)

- Confirmed that low β-amyloid in CSF is associated with positive amyloid on scan

- *Amyvid* approved by FDA in April 2012
  - Not yet covered by insurance payers
**Amyloid Imaging in MCI**

_Average_ MCI group deposition of PiB is significantly greater than controls.

In _INDIVIDUAL CASES_, PiB deposition is either elevated or in the range of normal controls.

![Graph showing PiB uptake in different brain regions for MCI and controls.](image)


**Prediction of Outcome Utilizing PiB Imaging in MCI:**

PiB+ Cases Develop AD; PiB- Cases Do Not

23/26 patients have had follow-up ADRC evaluations

- Mean f/u: 24.0 months (6-57 months)

13 PiB positive
- (Mean f/u: 23.6 months)

10 PiB negative
- (Mean f/u: 24.5 months)

Wolk, et al., 2009
Can we identify people who have the AD pathology in their brains \textit{before} any thinking or memory problems develop?

Average Cortical PIB Binding in Cognitively Normal Controls and AD (41 subjects)
Change in Amyloid Imaging (PiB) in a Control over Two Years

Variability of Amyloid Binding in Asymptomatic Normal Elderly

Courtesy of Reisa Sperling, Harvard Univ.
Amyloid Plaque (PiB Binding) in Normal Aging

\[ r = .37, p < .001 \]

Similar data from Australia (AIBL study), University of Pittsburgh, Mayo Clinic, Washington University, London,...others.


Summary

• Structural Imaging (MRI) will aid clinical measures for
  – Diagnosis
  – Prognosis in evaluation of MCI
  – Identifying pre-symptomatic disease for prevention
  – Monitoring therapeutic interventions

• Screening for clinical trials: AD, MCI, Prevention
  – Assure the disease is AD
  – Speed up studies

• Biomarkers will likely be important in all future studies
Future Therapy

- **Symptomatic improvement** (cognitive and behavioral)

- **Non-specific** therapies
  - Antioxidants, Anti-inflammatory agents, others
  - None so far successful

- Therapies directed at **specific** pathology:
  - Anti-amyloid therapy
  - Anti-neurofibrillary tangle strategies
  - Genetics-guided interventions

Evidence of removal of amyloid plaque from brains of patients with AD treated with bapineuzumab:

A phase 2, double-blind, placebo-controlled, ascending-dose study

Rinne et al., Lancet Neurology 2010
Loss of amyloid on PET Scan—how much is enough?

Rinne et al., Lancet Neurology 2010

Revised Diagnostic Criteria

Recommendations from the NIA/Alzheimer’s Association Workgroup

- Pre-Clinical AD
- Mild Cognitive Impairment
- Alzheimer’s Disease

Prevention of Alzheimer’s

- Actions to prevent dementia or delay its onset
- Identify and treat presymptomatic persons with disease-modifying medications to delay onset of symptoms of dementia
- Not all prevention is medication based...
  - Vascular risk factors: HBP, lipids, diabetes
  - Exercise
  - Lose weight
  - Engage in mental activities
  - Broad range of social interactions
  - Play games!

Prevention of Alzheimer’s

- All prevention trials either negative (Ginkgo GEM trial; DeKosky et al, 2009) or stopped for toxicity (ADAPT, NSAIDs; WHIMS (estrogen, estradiol))
- Barring breakthrough in design, such studies will take years to complete
- Treatments will probably be more effective earlier in the disease course
National Alzheimer’s Project Act

- Passed by Congress in 2011
- Forms national committee to assemble and report to the nation the status of AD in the country
- Will there be funds to support the initiatives identified by the NAPA Committee?